

# PATENT COOPERATION TREATY

PCT

## NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Assistant Commissioner for Patents  
United States Patent and Trademark  
Office  
Box PCT  
Washington, D.C.20231  
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing: 02 November 2000 (02.11.00)	
International application No.: PCT/US00/10954	Applicant's or agent's file reference: DALHO1340WO
International filing date: 21 April 2000 (21.04.00)	Priority date: 23 April 1999 (23.04.99)
Applicant: LEE, Song, F. et al	

1. The designated Office is hereby notified of its election made:

☒ in the demand filed with the International preliminary Examining Authority on:  
26 September 2000 (26.09.00)

☐ in a notice effecting later election filed with the International Bureau on:  
\_\_\_\_\_

2. The election ☒ was

☐ was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No.: (41-22) 740.14.35	Authorized officer:  J. Zahra Telephone No.: (41-22) 338.83.38
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## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US00/10954

## A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : A61K 35/00, 48/00, 39/00; C12N 1/20

US CL : 424/93.1, 184.1; 514/44; 435/253.4

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/93.1, 184.1; 514/44; 435/253.4

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched  
NONEElectronic data base consulted during the international search (name of data base and, where practicable, search terms used)  
WEST, BIOSIS, MEDLINE, CAPLUS

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	HOMONYLO-MCGAVIN et al. Role of C terminus in antigen P1 surface localization in Streptococcus mutants and two related cocci. February 1996. J. Bacteriology. Vol. 178. No. 3. pages 801-807. See entire article.	1-4 and 10-12
X	OGGIONI et al. Immunization of mice by oral colonization with live recombinant commensal streptococci vaccine. 1995. Vaccine. Vol. 13. No. 8. pages 775-779. See page 778, column 1; page 776 column 1, paragraph 2; page 779, column 2, last paragraph.	1-4, 10, 11, 13-16, 22-26 and 32

☒ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A" document defining the general state of the art which is not considered to be of particular relevance	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E" earlier document published on or after the international filing date	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&" document member of the same patent family
"O" document referring to an oral disclosure, use, exhibition or other means	
"P" document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

11 JULY 2000

Date of mailing of the international search report

28 AUG 2000

Name and mailing address of the ISA/US  
Commissioner of Patents and Trademarks  
Box PCT  
Washington, D.C. 20231

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## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US00/10954

## C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	BOUCHER et al. Neutralizing antibodies and immunoprotection against Pertussis and Tetanus obtained by the use of a recombinant pertussis toxin-tetanus toxin fusion protein. February 1994. Infection and Immunity. Vol.62. No. 2. Pages 449-456. See entire article.	1-35
A	CRYSTAL et al. Transfer of Genes to Humans: Early lessons and obstacles to success. 1995. Science. Vol. 270. pages 404-410. See entire article.	1-35

## PATENT COOPERATION TREATY

## PCT

## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

REC'D 10 JUL 2001

WIPO

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Applicant's or agent's file reference DALH01340WO	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/US00/10954	International filing date (day/month/year) 21 APRIL 2000	Priority date (day/month/year) 23 APRIL 1999
International Patent Classification (IPC) or national classification and IPC IPC(7): A61K 35/00, 48/00, 39/00; C12N 1/20 and US Cl.: 424/93.1, 184.1; 514/44; 435/253.4		
Applicant DALHOUSIE UNIVERSITY		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 6 sheets.
- ☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority. (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of 2 sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☐ Non-establishment of report with regard to novelty, inventive step or industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability, citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☒ Certain observations on the international application

Date of submission of the demand 26 SEPTEMBER 2000	Date of completion of this report 04 JUNE 2001
Name and mailing address of the IPEA/US Commissioner of Patents and Trademarks Box PCT Form PCT/IPEA/416 (July 1998)★ Washington, D.C. 20531	Authorized officer MICHAEL C. (Y01301) 0196 <i>Michael C. Allen for</i>

## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/US00/10954

**I. Basis of the report**

## 1. With regard to the elements of the international application:\*

☒ the international application as originally filed☒ the description:pages 1-40, as originally filedpages NONE, filed with the demandpages NONE, filed with the letter of \_\_\_\_\_☒ the claims:pages 41-45, as originally filedpages NONE, as amended (together with any statement) under Article 19pages NONE, filed with the demandpages NONE, filed with the letter of \_\_\_\_\_☒ the drawings:pages 1-3, as originally filedpages NONE, filed with the demandpages NONE, filed with the letter of \_\_\_\_\_☒ the sequence listing part of the description:pages NONE, as originally filedpages NONE, filed with the demandpages NONE, filed with the letter of \_\_\_\_\_2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language \_\_\_\_\_ which is:

☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).☐ the language of publication of the international application (under Rule 48.3(b)).☐ the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:☐ contained in the international application in printed form.☐ filed together with the international application in computer readable form.☐ furnished subsequently to this Authority in written form.☐ furnished subsequently to this Authority in computer readable form.☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.4. ☒ The amendments have resulted in the cancellation of:☒ the description, pages NONE☒ the claims, Nos. NONE☒ the drawings, sheets/fig NONE5. ☐ This report has been drawn as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).\*\*

\* Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).

\*\*Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.

## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/US00/10954

**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement****1. statement**

Novelty (N)	Claims <u>5-9, 17-21, 27-31</u>	YES
	Claims <u>1-4, 10-16, 22-26 and 32-35</u>	NO
Inventive Step (IS)	Claims <u>5-9, 17-21 and 27-31</u>	YES
	Claims <u>1-4, 10-16, 22-26 and 32-35</u>	NO
Industrial Applicability (IA)	Claims <u>1-35</u>	YES
	Claims <u>none</u>	NO

**2. citations and explanations (Rule 70.7)**

Claims 1-4 and 10-12 lack novelty under PCT Article 33(2) as being anticipated by Homonylo-McGavin.

Homonylo-McGavin teaches a composition comprising the P1 deficient *S. mutans*, *S. gordonii* and *E. faecalis*, expressing the full length P1 gene or spaP protein, carried on the shuttle plasmid pSM1/II-3, generated by cloning the spaP gene from sSM1/II into the *E. coli* streptococcus shuttle vector pDL276, was localized on the cell surface of the transformants. Thus, Homonylo-McGavin taught a composition comprising *S. mutans*, *S. gordonii*, and *E. faecalis*, live commensal organisms, genetically modified by being deficient in P1, and expressing at least one immunogenic fragment, the spaP protein as claimed.

Claims 1-4, 10, 11, 13-16, 22-26 and 32-35 lack novelty under PCT Article 33(2) as being anticipated by Oggioni.

Oggioni teaches using recombinant streptococci as live vaccine vectors, using *S. gordonii* expressing heterologous cell-surface antigens. Wild type *S. gordonii*, a recombinant *S. gordonii* expressing the M6 fibrillar surface protein of *S. pyogenes*, and a recombinant expressing the E7 protein of human papilloma virus type 16 as a fusion with the M6 protein ( see abstract). Oggioni also teaches that in outbred mice, the human oral commensal *S. gordonii* was effectively colonized in said mice, and induced a systemic immune response for surface expressed foreign proteins (page 778, 1st col). Oggioni further teaches that *S. gordonii* strains of this live inoculum was given to mice, administered intra nasally and orally, wherein each mouse received about  $1 \times 10^9$  c.f.u. of bacteria (page 776, left col, 2nd para). Finally, Oggioni teaches that outbred mice can be stably colonized by a single intranasal/oral inoculum of *S. gordonii*; recombinant strains are equally effective as wild-type in colonizing mice; two months after inoculum, 83% or animals are still positive for the isolation of *S. gordonii*; recombinant *S. gordonii* are always positive for expression of the heterologous antigens; live bacteria induced a systemic immune response, which depended upon the effective colonization by live bacteria, since killed bacteria do not induce such a response; and finally, that these results indicate that recombinant (Continued on Supplemental Sheet.)

**VIII. Certain observations on the international application**

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

The description is objected to under PCT Rule 66.2(a)(v) as lacking clarity under PCT Article 5 because it fails to contain an adequate written description of immunogenic fragments. The description is inadequate because: the meaning of the term immunogenic fragment is the meaning of the term in the ordinary usage in the art. The disclosure and claims do not indicate what it means by immunogenic fragments, and whether or not the term means a protein having one or more amino acid substitutions, deletions, insertions, and/or additions made to the immunogenic fragment of the pertussis toxin comprising the N-terminal 179 amino acids of the S1 subunit of the pertussis toxin. The disclosure and claims do not indicate what distinguishing attributes are shared by members of the genus. The disclosure and claims do not place any limit on the number of amino acid substitution, deletions, insertions and/or additions which may be made to the subunit of the pertussis toxin. Thus the scope of the claims includes numerous structural variants, and the genus is highly variant because a significant number of structural differences between genus members is permitted. Although the disclosure states that these types of changes are routinely done in the art, and the DNA sequences coding for these antigens are either available from GenBank or from publications, the disclosure and claims do not provide any guidance as to what changes should be made. Structural features that could distinguish compounds in the genus from others in the protein class are missing from the disclosure. No common structural attributes identify the members of the genus. The general knowledge and skill in the art do not supplement the omitted description because specific, not general guidance is what is needed. Since the disclosure fails to describe the common attributes or characteristics that identify the members of the genus, and because the genus is highly variant, an immunogenic fragment of the pertussis toxin comprising the N-terminal 179 amino acids of the S1 subunit of pertussis toxin alone is insufficient to describe the genus.

According to the disclosure, the term live oral commensal organism means that the native organism, once acquired in infancy, persists in a mammalian host in the oral cavity under normal conditions, throughout childhood and into adulthood.

The disclosure teaches only one live commensal organism within the scope of the genus *Streptococcus*, *S. gordonii*. There is no description of how *S. gordonii* relates to the structure of any strictly neutral live commensal organism. The general knowledge in the art concerning live oral commensal organisms does not provide any indication of how the structure of one *Streptococcus* is representative of unknown live commensal oral organisms. The nature of live commensal oral organisms is that they are highly variant structures, and in the present state of (Continued on Supplemental Sheet.)

**Supplemental Box**

(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: Boxes I - VIII

Sheet 10

**V. 2. REASONED STATEMENTS - CITATIONS AND EXPLANATIONS (Continued):**

commensal streptococci are candidates as vaccines (page 778, last para).

Claims 5-9, 17-21 and 27-31 meet the criteria set out in PCT Article 33(2)-(4), because the prior art does not teach or fairly suggest a composition for the stimulation of protection against infection comprising a live commensal organism genetically modified to express at least one immunogenic fragment of said pathogen, wherein the pathogen is *Bordetella pertussis*, or methods for prophylactically treating a host against infection or chronic immunization of host via said composition in mice.

## ----- NEW CITATIONS -----

NONE

**VIII. CERTAIN OBSERVATIONS ON THE APPLICATION (Continued):**

the art, the structure of one does not provide guidance to the structure of others. The common attributes of the genus are not described. Thus, the ordinary artisan would conclude that applicant was not in possession of the claimed genus because a description of only one member of this genus is not representative of the variants of the genus and is insufficient to support the claim.

Claims 1-32 are objected to as lacking clarity under PCT Rule 66.2(a)(v) because practice of the claimed invention is not adequately described in writing, as required under PCT Rule 5.1(a)(iii), for the reasons set forth in the immediately preceding paragraph.

The description is objected to under PCT Rule 66.2(a)(v) as lacking clarity under PCT Article 5 because it fails to adequately enable practice of the claimed invention because:

The examples and results on pages 24-40 shows that applicant was successful in constructing a fusion protein between the *S. mutans* antigen, SpaP or P1 antigen, and the *B. pertussis* PT S1 subunit which was later introduced into *S. gordonii* by natural transformation; in demonstrating the expression and localization of the SpaP-S1 fusion protein in *S. gordonii*, indicating that the cell fusion protein was cell surface localized in *S. gordonii*; and in showing that recombinant S1 was immunogenic, and that it can induce protective antibodies in vivo. Applicant was also successful in demonstrating that mice orally colonized and eliciting a protective immune response to recombinant *S. gordonii* by expressing S1 fragment, maintained the recombinant bacterium for a minimum of 10 months, in 8 out of 12 colonized mice, indicating that oral colonization can be achieved.

However, it is not readily apparent that a skilled artisan given applicant's disclosure alone, would be able to practice the invention over the scope claimed in view of the lack of guidance provided in the disclosure as filed. In the instant situation, the claims embrace any pathogen and any genetically modified commensal oral organism. The disclosure gives specifics only for the pathogen, PT 1 subunit of the *B. pertussis*, and the genetically modified oral commensal organism, *S. gordonii*. It remains unclear that the state of the art regarding oral compositions or vaccines for the stimulation of protection against infection, was such that one skilled in the art would have been able to routinely confer protection against infection by any pathogen, by utilizing any genetically modified live commensal oral organism expressing at least one immunogenic fragment of any pathogen, as broadly claimed. Such is considered to require undue experimentation.

The disclosure is not enabling because it fails to teach how one would identify the immunogenic fragments of pathogens selected, in the absence of amino acid sequences. How would one determine which aspect of the amino acid sequence would be considered immunogenic, or how would one determine whether or not the immunogenic fragment when folded or after post-translational modification, would retain its immunological properties such that epitopes to which specific antibodies bind would be recognized, and how would one test each immunogenic fragment for toxicity against the genetically modified oral commensal organism selected(GMOC)?

Likewise, the disclosure is not enabling because it fails to teach how many unmodified species would be allowed to co-exist with the genetically modified oral commensal organisms(GMOC), and whether or not this inversion in the ratio of unmodified live commensal organisms to GMOCs would introduce morbidity in hosts when the composition is administered.

Similarly, the disclosure fails to teach how often, if any, a booster shot would be administered, and if so, under what circumstances. No mention is made of the specific components and quantities of the vaccine composition, neither is mention made of how pathogens would be selected, prepared, and the cost involved and what would be the potential side effects of this oral vaccine. No mention is made of the correlation between the mouse model and other hosts in terms of long-term stability and expression of the GMOs. How long would the GMOs colonize the oral cavity in other hosts and would the expression be sufficient and stable to confer protection beyond the 10 months as recorded in the mouse model? Further, the claims embrace



**Supplemental Box**

(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: Boxes I - VIII

Sheet 11

being able to protect against any pathogen. However, humans are not simply large mice in that there have been several surprise examples in which predictions from studies conducted in experimental animals have not been borne out in human safety and efficacy trials. Furthermore, it has become apparent that studies in experimental animals may not necessarily predict toxicology in humans. Therefore, human hosts if orally colonized, may not retain the recombinant GMO for the length of time as predicted by the mouse studies.

The physiological art of utilizing compositions for the stimulation of protection against infection by at least one pathogen comprising a live commensal organism, genetically modified to express at least one immunogenic fragment of said pathogen, because pertussis toxin S1 subunit had been fused to tetanus toxin to yield the recombinant hybrid protein which was produced in *E. coli* and non-toxic, immunogenic and elicited an immunoprotective response against tetanus and pertussis in mice and guinea pigs. However, the physiological art of utilizing compositions for the stimulation of protection against infection comprising a live oral commensal organism such as *Streptococcus*, for prophylactically treating a human host against infection by a pathogen and for chronic immunizations would have been considered unpredictable.

In the absence of specific guidance which is lacking in the disclosure as filed, and given the state of the art at the time of filing, coupled with the reasons discussed above, it would require undue experimentation for the skilled artisan to practice the methods or use the claimed products.

The quantity of experimentation required to practice the invention as claimed would require the selection of a pathogen, the determination of the immunogenic fragment of said pathogen, which when expressed by any genetically modified live commensal oral organism, would be expressed in therapeutically effective amounts, and would be stable indefinitely in the oral cavity such that colonization, followed by expression leading to protection against infection would be maintained in a host. This is considered trial and error experimentation as one must select from the innumerable genus of live commensal oral organisms, species, which when genetically modified, would express any pathogen to confer protection and prevent infection in any host, including humans. This is an invitation to experimentation and as such is considered undue.

Claims 1-32 are objected to as lacking clarity under PCT Rule 66.2(a)(v) because practice of the claimed invention is not enabled as required under PCT Rule 5.1(a) for the reasons set forth in the immediately preceding paragraph.

Claims 2-12 and 14-32 are objected to under PCT Rule 66.2(a)(v) as lacking clarity under PCT Article 6 because the claims are indefinite for the following reason(s): Claims 2-12, 14-22, and 23-32, are considered vague and indefinite for use of the indefinite article "A" at the beginning of the preamble instead of the definite article "The". "A" is generally reserved for independent claims, and since the delineated claims are all dependent upon preceding claims, the definite article "The" which is reserved for dependent claims, should be used instead. The scope of the preamble as recited is unclear, since use of the indefinite article "A" does not necessarily indicate the scope of the method is limited to that set forth in the method of the independent claim 1. Claims are objected to for use of the indefinite article "The" at the beginning of the preamble, instead of the definite article "A".

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